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Health and Environmental Effects Profile for MCPA and MCPB

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16. ABSTRACT

The Health and Environmental Effects Profile for MCPA and MCPB was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. MCPA and MCPB have been determined to be systemic toxicants. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for MCPA is 1.0×10^{-2} (mg/kg bw/day) and for MCPB is 1×10^{-2} (mg/kg bw/day) for oral exposure.

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January 1984

HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR MCPA AND MCPB

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

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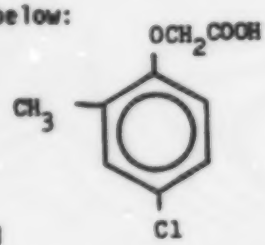
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
BUN	Blood urea nitrogen
bw	Body weight
DNA	Deoxyribonucleic acid
GC	Gas chromatography
GI	Gastrointestinal
HPLC	High-performance liquid chromatography
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
MS	Mass spectrometry
NOEL	No-observed-effect level
ppb	Parts per billion
ppm	Parts per million
SGOT	Serum glutamic-oxaloacetic transaminase
TLC	Thin-layer chromatography
w/w	Weight per weight

1. INTRODUCTION

1.1. STRUCTURE AND CAS REGISTRY NUMBER

2-Methyl-4-chlorophenoxyacetic acid (MCPA) is also known as MCP, 4-chloro-o-cresoxyacetic acid and ((4-chloro-o-tolyl)oxy)acetic acid. The structure of MCPA is given below:

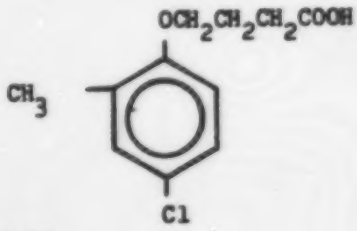


Empirical formula: $C_9H_9O_3Cl$

Molecular weight: 200.62

The Chemical Abstracts Service (CAS) Registry number for MCPA is 94-74-6.

4-(4-Chloro-2-methylphenoxyl)butyric acid (MCPB) is also known as 4-(4-chloro-2-methylphenoxy)butanoic acid, gamma-(4-chloro-2-methylphenoxy) butyric acid and 2-methyl-4-chlorophenoxybutyric acid. It has the following structure:



Empirical formula: $C_{11}H_{13}O_3Cl$

Molecular weight: 228.68

The Chemical Abstracts Service (CAS) Registry number for MCPB is 94-81-5.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Both MCPA and MCPB, when pure, are white crystalline compounds; however, they are available commercially as the free acids and as salts and esters. The physical properties of MCPA and MCPB are listed in Tables 1-1 and 1-2, respectively. MCPA acid will be dissociated $\geq$99% at pHs >5 and MCPB will be dissociated $\geq$99% at pHs $\geq$7. Stevens and Grorud (1979) identified a number of the impurities in commercial MCPA (Table 1-3).

TABLE 1-1

Physical Properties of MCPA*

Melting point:	118-119
Density:	0.6 g/cc
Water solubility:	1500 ppm at 25°C 825 ppm at 15°C
Solvent solubility (g/100 g solvent):	
ethanol	153
ethyl ether	77
toluene	6.0
xylene	5.0
n-heptane	0.5
pK_a	3.13 (Cessna and Grover, 1978)

*Source: U.S. EPA, 1982

TABLE 1-2

Physical Properties of MCPB

Melting point	100	Plimmer, 1980
Water solubility	44 ppm	Plimmer, 1980
pK_a	4.80	Nelson and Faust, 1969

TABLE 1-3

Analysis of Commercial MCPA*

Compound	Nominal % in MCPA
Phenolic Impurities	
2-Methyl phenol	0-0.1
3-Methyl phenol	0-0.1
2-Chlorophenol	0-0.1
4-Chlorophenol	0-0.1
2-Chloro-6-methyl phenol	0-0.1
4-Chloro-2-methyl phenol	0-0.5
4-Chloro-3-methyl phenol	0-1
4-Chloro-2,6-dimethyl phenol	0-0.5
2,4-Dichloro-6-methyl phenol	0-0.5
MCPA	90-99
Phenoxy Acid Impurities	
2-Methylphenoxyacetic acid	0-2.5
3-Methylphenoxyacetic acid	0-0.5
2-Chlorophenoxyacetic acid	0-0.5
4-Chlorophenoxyacetic acid	0-0.5
2-Chloro-6-methyl phenoxyacetic acid	0-4
4-Chloro-2,6-dimethylphenoxyacetic acid	0-0.5
2,4-Dichloro-6-methylphenoxyacetic acid	0-3
MCPA	90-100

*Source: Stevens and Grorud, 1979

1.3. PRODUCTION DATA

MCPA is produced by Diamond Shamrock Corp. in Tuscaloosa, AL; Dow Chemical Co. USA in Midland, MI; Rhone-Poulenc, Inc. in Portland, OR; Riverdale Chemical Co. in Chicago Heights, IL; and Union Carbide Corp. in St. Joseph, MO (SRI International, 1983). MCPB is produced by Rhone-Poulenc, Inc. in Portland, OR (SRI International, 1983). SRI (1976) estimated that 3.9 million pounds of MCPA and 0.1 million pounds of MCPB were produced in 1975. MCPA is produced by reacting 4-chloro-o-cresol with sodium chloroacetate in alkaline solution (BCPC, 1977). MCPB is made by reacting the sodium salt of 4-chloro-o-cresol with butyrolactone.

1.4. USE

Both MCPA and MCPB are hormone type herbicides that are effective against broadleaf plants in cereals, peas and established grasslands (BCPC, 1977). Both products are used as the acids, sodium salt, amine salts and esters.

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. AIR

Pertinent data regarding the atmospheric chemistry of MCPA or MCPB were not located in the available literature. Hendry and Kenley (1979) have presented the rate constants and estimated half-lives for reaction with hydroxyl radical of several alkyl- and fluoro-substituted benzenes, anisole and o-cresol, which have similarities in structure. Based on these values, both MCPA and MCPB would be expected to have an atmospheric half-life of <1-10 days. A similar estimation for reaction with ozone is more difficult, since fewer data for this reaction were presented in Hendry and Kenley (1979); however, based on their data, the half-life for both compounds would probably be <10 days.

Pertinent data regarding the vapor phase photolysis of MCPA or MCPB were not located in the available literature. Que Hee and Sutherland (1979) photolyzed 2,4-dichlorophenoxyacetic acid butyl ester (2,4-D butyl ester) under simulated environmental conditions. The ester was in both the pure liquid and vapor phase. The authors reported an approximate half-life of 300 hours given the similarities in structure, a half-life of the same order would be expected for MCPA and MCPB.

The vapor phase transport of MCPA and MCPB in air will not be an important process for the free acids or their salts because of their low vapor pressure. The esters of these acids, however, are volatile to varying degrees and can be transported long distances in the vapor phase. In addition to vapor phase transport, spray droplet transport will be a factor with these herbicides, since they are sometimes applied by spray. However, spray drift generally is limited to a few kilometers (Bogyo et al., 1981).

Pertinent data regarding the vapor drift of MCPA and MCPB esters were not located in the available literature. Considerable information, however, is available for 2,4-D esters; these esters have densities and other physical properties similar to MCPA and MCPB esters, and would be expected to behave in an analogous fashion. A number of factors influence the vapor drift of chlorophenoxy herbicides, including the surface area of the herbicide exposed to air, the absorptive and adsorptive characteristics of the surface to which the ester is adhering, the vapor pressure of the ester, the carrier solvent and the additives present in the mix (Bogyo et al., 1981). In general, the esters with lower molecular weights are more volatile (i.e., they have higher vapor pressure). Vapor pressures for the esters of 2,4-D vary from 10^{-3} torr for the methyl ester to $<10^{-6}$ torr for the esters with higher molecular weights (Jensen and Schall, 1966; Hamaker and Kerlinger, 1969; Flint et al., 1968; Kybett et al., 1976). The distances traveled by ester vapors appear to be on the order of "tens of miles" (Reisinger and Robinson, 1976, 1977) for the highly volatile esters. This transport is dependent on weather conditions and is aided by weak frontal systems. Grover et al. (1976) reported that the highest atmospheric concentrations of chlorophenoxy herbicide esters came in the spraying season and that low concentrations were present during or immediately after rain (this indicates that these esters are washed out of the air). (See Appendix for literature searched; also additional classified information is available. See Chapter 8 for a more complete explanation.)

2.2. WATER

The only important aqueous chemical process for MCPA and MCPB ester is hydrolysis. Pertinent data regarding the rates for this process were not located in the available literature; however, Mill (1980) reported on the

hydrolysis of 2,4-D butyl ester. At pH 4, the half-life is on the order of 2 years, while at pH 7, the half-life is ~8 days. A similar type of pH-hydrolysis half-life relationship is expected for MCPA and MCPB esters, since they have similar structures. Zepp et al. (1975) used theoretical considerations and structure-activity relationships to estimate the hydrolysis half-lives of 2,4-D esters. They reported the half-lives for the methyl, isopropyl, n-butyl, n-octyl, isooctyl and butoxyethyl esters to be 44, 710, 220, 220, 1500 and 26 days, respectively, at pH 6, while at pH 9 the half-lives were 1.1, 17.0, 5.2, 5.2, 37 and 0.6 hours, respectively. Rodgers and Stalling (1972) reported that the addition of fish to an aquarium decreased the hydrolysis half-life of 2,4-D butoxyethyl ester from ~40 to <4 days. Again, a similar behavior is expected for MCPA and MCPB, in that the esters with higher molecular weights will hydrolyze more slowly than those with low molecular weights, and that fish will decrease the hydrolysis half-lives of esters in water. Nevertheless, exact half-lives for MCPA and MCPB esters cannot be estimated from these data; however, since the esters have similar structures, the half-lives are probably on the same order of magnitude.

Soderquist and Crosby (1975) reported that when MCPA was photolyzed in water using fluorescent light (>290 nm, pH 9.8), 4-chloro-2-methylphenol, 4-chloro-2-formylphenol and o-cresol were formed. Also, Strekozov et al. (1979) reported formation of 4-chloro-2-methylphenol when MCPA was photolyzed. At pH 8.3, the half-life of MCPA in sunlight is 20-24 days (Soderquist and Crosby, 1975).

Virtanen et al. (1979) studied MCPA dissipation in a model ecosystem containing water, soil, sand, three genera of plants, fish, mice and snails. MCPA sodium salt was sprayed on the soil and watered three times during the study. MCPA concentrations declined in the soil (0.196 to 0.114 ppm) over

12 days, but increased in the water (0.045 to 0.156 ppm). After 22 days, 20% of the applied MCPA remained. Soderquist and Crosby (1975) reported that MCPA in rice paddy water in the dark was 99% removed within 14 days by aquatic organisms after application of 0.98 kg/ha MCPA dimethylamine salt. (See Appendix for literature searched; also additional classified information is available. See Chapter 8 for a more complete explanation.)

2.3. SOILS

The great majority of information regarding MCPA and MCPB concerns its behavior in soils. Biodegradation appears to play a dominant role, although hydrolysis and volatilization of MCPA and MCPB esters will occur. Sorption increases with increasing organic matter and decreasing pH.

MCPA appears to be degraded rapidly in most soils, with half-lives varying from a few days to ~1 month in both laboratory and field studies (Kirkland and Fryer, 1972; Soulas et al., 1983; Stark, 1983; Smith and Hayden, 1980; Sattar, 1982; Sattar and Paasivirta, 1980; Torstensson et al., 1975; Smith and Hayden, 1981; Smith, 1982). Dissipation to below the detection limits requires a longer period varying from 4 days (Kirkland and Fryer, 1972) to over 32 weeks (Sattar, 1982). Variations depend on a number of factors, including application rates (higher concentrations give slower removal rates), whether or not the soil has been previously treated with chlorophenoxy herbicides (previous treatment increases dissipation rates), organic matter content (higher organic matter content lowers removal rates), soil moisture (low moisture content slows degradation), temperature (higher temperatures increase degradation rates), and soil pH (degradation is most rapid between pH 5.5-8.5). For the most part, however, it appears that the magnitude of these variations are such that degradation rates will be independent of soil type and bacterial population (Loos et al., 1979).

Much less information was found for MCPB; however, two studies indicated that MCPB behaves virtually identically to MCPA (Smith and Hayden, 1981; Kirkland and Fryer, 1972).

MCPA is expected to be mobile in most soils. Helling (1971) and Helling and Turner (1968), using soil TLC, reported that MCPA was mobile (R_f 0.6-1.0) on chillium silt loam (3.1% organic matter), Lakeland sandy loam (0.9% organic matter) and Hagerstown silty clay loam (1.4% organic matter) soils. Herzel and Schmidt (1979) reported that phytotoxic levels of MCPA leached 30 cm in a sandy loam column eluted with 50 cm of water. Despite its leachability, MCPA has only rarely been detected in groundwater. In 237 wells in Ontario, Canada, sampled between 1969 and 1978 (393 samples), MCPA was present in only two (Frank et al., 1979). One was contaminated between 1.1-10 ppb, the other between 1001-10,000 ppb. MCPA entered the wells either from direct spills of concentrate into the well or from spray drift. Leaching was not the cause of either positive result. An accidental spill of a 40% solution of MCPA (1000ℓ) in Czechoslovakia resulted in MCPA contamination of wells 150 miles from the spill site. Concentrations from 0.1-6.4 ppm were detected and persisted from 8-11 months after the spill. The lack of information concerning detectable residues of MCPA or MCPB in groundwater may be because of its rapid biodegradation (see above); however, there is insufficient information concerning use and use patterns to permit a more positive conclusion about the leaching potential of MCPA and MCPB.

A number of the metabolites of MCPA have been determined both from pure microbial cultures and from field studies. Gaunt and Evans (1971a,b) and Gamar and Gaunt (1971) found that a soil Pseudomonad (N.C.I.B. 9340, National Collection of Industrial Bacteria) and cell-free extracts prepared from this bacterium metabolized MCPA, yielding, initially, 5-chloro-o-cresol

and 5-chloro-3-methyl catechol. Further work suggested the following metabolic pathway: MCPA → 5-chloro-o-cresol → 5-chloro-3-methylcatechol → cis-cis-γ-chloro-α-methylmuconate → γ-carboxymethylene-α-methyl-ΔαB-butenolide → γ-hydroxy-α-methylmuconate. 4-Chloro-o-cresol was identified as a product of a soil bacterium, Flavobacterium peregrinum, by Bollag et al. (1967) and a soil Pseudomonas sp. by Kilpi et al. (1980, 1983). Sattar (1981) also identified this compound as well as 5-chloro-3-methylcatechol in whole soils treated with MCPA. Bollag et al. (1967) also reported that an Arthrobacter sp. isolated from soil could dehalogenate MCPA and several catechols. Kilpi et al. (1980) reported isolating 2-hydroxymuconic acid when a Pseudomonas sp. HV3 was incubated with MCPA. Alcaligenes saradoxus has also been reported to metabolize MCPA (Fisher et al., 1978; Jensen and Petersen, 1952a,b; Steenson and Walker, 1956).

Several researchers (Faulkner and Woodcock, 1965; Nakajima et al., 1973; Torstensson et al., 1975) have reported that fungi, Aspergillus niger, Fusarium culmorum, Gloeosporum kaki, G. olivarum, Mucor sp., Penicillium sp., Schizophyllum commune, Verticillium spp. and Zygorhynchus moelleri, metabolize MCPA; 4-chloro-5-hydroxy-2-methylphenoxyacetate and 2-(2-methyl-4-chloro-phenoxy)ethanol are two metabolites.

Pertinent data regarding the metabolic transformation pathways of MCPB were not located in the available literature; however, since MCPA and MCPB are structurally similar, it is anticipated that MCPB will degrade similarly. (See Appendix for literature searched; also additional classified information is available. See Chapter 8 for a more complete explanation.)

3. EXPOSURE

3.1. AIR

Pertinent data regarding MCPA or MCPB concentrations in the atmosphere were not located in the available literature. It is likely that concentrations will be highest during early spring when MCPA and MCPB are used as preemergence herbicides. (See Appendix for literature searched; also additional classified information is available. See Chapter 8 for a more complete explanation.)

3.2. WATER

A number of researchers have reported finding MCPA in ambient waters, while no reports were found confirming the presence of MCPB.

Konasewich et al. (1978) reported detecting MCPA as well as other phenoxy herbicides in the water of Lakes Erie and Huron. No MCPA was reported found in the sediment, air, discharges and sewage sludge, benthos, plankton, fish or wildlife within the Great Lakes Basin.

Frank et al. (1979) reported the levels of MCPA present in eight agricultural watersheds in Ontario in 1974. MCPA was present in only 2 of 98 samples (<0.1-1.7 µg/ℓ). Between 1975 and 1977, Frank and Sirons (1980) monitored 11 agricultural watersheds in Ontario. Of 949 stream waters analyzed, MCPA was detected six times. MCPA was used in 7 of the 11 watersheds, and was detected in streams draining both loam and sand soils. Concentrations ranged between <0.1-0.3 µg/ℓ. MCPA was used to control 54.2% of pea hectarage and 10.2% of cereal hectarage. Positive samples coincided with spraying operations. Losses in 1975 could be attributed to spray drift or careless handling. No MCPA was detected in 1976, and none was detected in rainwater samples or stream bed sediments.

Frank et al. (1979) detected MCPA in 2 of 237 wells in Ontario. The levels present were 1.1-10 ppb in one and between 1001-10,000 ppb in the other; however, these were the result of direct spills and not of leaching. MCPA was not listed as having been found in whole water in STORET, and MCPB was not listed at all. Since these herbicides have been detected only infrequently and then close to the source of contamination, it appears that human exposure to MCPA and MCPB in water will not be widespread.

3.3. SOIL

Very little information concerning soil residues was found in the available literature. Raatikainen et al. (1979) reported that ground application of an ester of MCPA at 0.25, 0.75 and 2.25 kg/ha resulted in a residue of 0.2, 0.8 and 3.0 mg/kg soil, respectively, ~35 days after application. Eronen et al. (1979) reported that birch leaves (with twigs) and moss showed 344 and 74 mg/kg residue, respectively, immediately after aerial application of 2.5 kg/ha of the isooctyl ester of MCPA. After 283 days, the birch leaves (with twigs) and moss showed residues of 32 and 0 mg/kg, respectively. In a laboratory experiment, Foster and McKerchen (1973) showed that MCPA had half-lives of 15-43 days in Saskatchewan soils. Given the paucity of residue information in the available literature, it is difficult to predict human exposure from soils; however, since the major use of MCPA appears to be in small grains, human exposure to MCPA and MCPB from soils does not appear to be high.

3.4. FOOD

No MCPA has been found in foods in the total diet samples reported by the Food and Drug Administration from July 1, 1969 to June 30, 1976 (Duggan et al., 1983). Earlier samples did report MCPA at levels ranging from 0.007-0.4 ppm (Corneliussen, 1969; Duggan et al., 1967). Since no recent reports are available for MCPA residues in food, and no residues have been reported since 1969, food does not appear to contribute to human MCPA and MCPB exposure.

4. PHARMACOKINETICS

4.1. ABSORPTION

Gurd et al. (1965) reported that MCPA is rapidly absorbed from the GI tract of rats and mice, but poorly absorbed through the skin of mice, even following damage to the skin. Excretion data indicate, however, that MCPA is absorbed dermally by rabbits (Section 4.4.) (Verschuuren et al., 1975). Elo (1976) reported rapid GI absorption of MCPA in rats following injection into the stomach; maximum tissue concentrations of MCPA were recorded within 2 hours after administration of the compound.

Metabolism data indicate that MCPB is absorbed by guinea pigs following oral administration (Section 4.3.) (Van Peteghem and Heyndrickx, 1975).

4.2. DISTRIBUTION

Elo (1976) administered [^{14}C]-MCPA (2-methyl-4-chlorophenoxy[1-^{14}C]-acetic acid) and non-labeled MCPA to rats by injection into the stomach at a level of ~11.5 mg/kg bw. All tissue concentrations were calculated on the assumption that [^{14}C] represented the unchanged acid. The highest concentrations of MCPA were found in the blood, kidneys, lungs, heart, suprarenal glands, liver, thyroid gland and bone marrow. The lowest concentrations of MCPA were found in the brain, adipose tissue, testis and muscle. At 5 days after treatment, measureable levels of MCPA (>0.05 µg [^{14}C]/g of wet tissue) were found only in the kidneys, liver and adipose tissue.

Elo and Ylitalo (1979) administered the sodium salt of [^{14}C]-MCPA (2-methyl-4-chlorophenoxy[1-^{14}C]acetic acid) to rats by subcutaneous injection at levels of 0, 25, 100, 250 or 500 mg/kg bw, followed by an intravenous injection of 8 mg/kg bw. All [^{14}C] activity in the tissues was assumed to represent unchanged [^{14}C]-MCPA. Pretreatment with MCPA in this manner resulted in increased [^{14}C] activity in the brain, cerebro-

spinal fluid, liver, muscle, heart and testis, and decreased [^{14}C] activity in the plasma and kidneys, but had no effect on [^{14}C] levels in the lungs. The MCPA concentrations in rat tissues at different times after a single subcutaneous administration of 250 mg sodium [^{14}C]-MCPA/kg bw are given in Table 4-1 (Elo and Ylitalo, 1979).

Whole body autoradiography was performed on pregnant mice given intravenous injections of [^{14}C]-MCPA (label location not specified) at a level of 0.8 mg/kg bw on day 15, 16, 17 or 18 of gestation (Lindquist, 1974). Detection of the vaginal plug was defined as day 0 of gestation. Animals were killed on day 18 of gestation. The radioactivity was uniformly distributed throughout the body in treated dams, with the highest concentrations occurring in the kidneys, visceral yolk sac and blood. Some radioactivity crossed the placenta, but fetal tissue concentrations were much lower than corresponding maternal tissue concentrations. The highest [^{14}C] concentration in the fetus occurred in the blood. There was no major site of [^{14}C] accumulation in fetal tissues. Within 48 hours after treatment, there was no retention of radioactivity in either dams or fetuses.

DeBeer et al. (1980) reported the case study of a 65-year-old female who ingested <1 ℓ of Argroxyl, a selective herbicidal aqueous formulation containing 250 mg/ℓ of MCPA sodium and potassium salts. The subject also consumed a large quantity of parathion, which was attributed as the cause of death (occurring within a few minutes; exact time of death not specified). The post mortem tissue levels of MCPA, measured by GC-MS, are given in Table 4-2.

4.3. METABOLISM

Rabbits given MCPA (80.6% pure) orally or dermally excreted the compound intact in the urine within 24 hours after dosing, but the amount was not

TABLE 4-1

MCPA Concentrations in Rat Tissues at Different Times After Subcutaneous Administration of 250 mg Sodium MCPA/kg bw[a]

	MCPA Concentrations (µg of acid/100 mg or µl of wet tissue)[b]									
Tissue	10 min	30 min	1 hr	2 hr	4 hr	8 hr	12 hr	24 hr	48 hr	120 hr
Plasma	25.7	47.3	55.2	64.1	62.5	59.5	52.5	39.5	20.2	0.7
Liver	7.0	24.5	30.5	37.2	39.8	32.0	27.6	19.0	7.2	0.7
Kidney	10.0	25.6	28.8	35.6	35.6	35.3	24.8	16.7	9.4	0.9
Brain[c]	0.5	2.0	4.3	8.6	11.1	7.4	5.5	2.4	0.4	0.0
Muscle	2.0	8.3	11.4	13.7	13.3	10.3	9.0	5.3	2.2	0.2
Testis	0.5	4.1	7.8	12.0	14.5	11.4	9.4	6.1	3.1	0.1

[a]Source: Elo and Ylitalo, 1979

[b]MCPA concentrations in the tissues were calculated on the basis of [^{14}C] activities. The means from two animals are given.

[c]Concentration in the brain is the mean of three different samples (forebrain, cerebellum and brain stem at the level of the pons).

min = minute

hr = hour

TABLE 4-2

Post Mortem Tissue Levels of MCPA in a 65-Year-Old Female Who Ingested MCPA Sodium and Potassium Salts*

Tissue	Concentration in mg %
Stomach content	312
Small intestine content	14.15
Blood	7.75
Kidneys	2.77
Liver	2.38
Muscle	0.70
Urine	0.36

*Source: DeBeer et al., 1980

quantified (Verschuuren et al., 1975). TLC analysis was performed only for the intact compound; therefore, no qualitative or quantitative metabolism data were reported.

Van Peteghem and Heyndrickx (1975) administered MCPB orally to one guinea pig and analyzed the 24-hour urine by GC-MS for MCPA. The presence of an unspecified amount of MCPA in the 24-hour urine indicated ω oxidation of the alkyl side chain of MCPB by the guinea pig. No original butyric acid derivative was detected in the 24-hour urine of the guinea pig.

4.4. EXCRETION

Elo (1976) reported rapid excretion of MCPA following administration of [^{14}C]-MCPA (2-methyl-4-chlorophenoxy[1-^{14}C]acetic acid) to rats by injection into the stomach at a level of ~11.5 mg/kg bw. Maximum tissue concentrations of MCPA were reached within 2 hours after administration and started to decrease rapidly starting at 8 hours after administration, with the exception of adipose tissue. Within 24 hours after dosing, 92.2% of the [^{14}C] was excreted in the urine and 6.76% was excreted in the feces. At 5 days after administration of [^{14}C]-MCPA, >100% of the [^{14}C] had been excreted in the urine and feces.

Senczuk and Pogorzelska (1981) also reported rapid excretion and/or disposition of MCPA by rats, as blood levels of MCPA were measureable for only 1 hour after dosing. No other details were provided in the available abstract of this study from the Polish literature.

Fjeldstad and Wannag (1977) measured the average urinary excretion of MCPA (by HPLC) from four males (ages 32-36 years; described as being healthy) who voluntarily ingested 5 mg of MCPA each. At 24, 48, 72 and 96 hours after administration of the compound, the average urinary excretion

was 40.7, 51.5, 53.7 and 55.0%, respectively, of the 5 mg ingested. After the 5th day, urinary excretion was <0.2 µg/mL (analytical detection limit).

A 65-year-old female who ingested an unknown amount of a weedkiller containing MCPA sodium and potassium salts excreted some of the compound in her urine (see Section 4.2.) (DeBeer et al., 1980).

The only data on excretion after dermal exposure was provided by Verschuuren et al. (1975) when an aqueous paste of MCPA was applied to the shaved skin of male rabbits (4 animals/group) at levels of 0, 0.5, 1.0 and 2.0 g/kg bw, 5 times a week for 3 weeks. It was reported that unchanged MCPA was detected in the urine by 24 hours, however, quantification was not performed.

5. EFFECTS

5.1. CARCINOGENICITY

A 64-year-old Finnish farmer exposed to MCPA developed acute aplastic anemia and subsequent acute myelogenous leukemia, culminating in death (Timonen and Palva, 1980; Palva et al., 1975).

Several studies examining the relationship between exposure to phenoxy-acetic acids, including MCPA, and cancer exist (Hardell, 1979; Hardell et al., 1981; Eriksson et al., 1981; Barthel, 1976). The subjects of these studies, however, usually were exposed to several other chemicals, including phenoxy-acetic acids other than MCPA that are more likely to contain polychlorinated dibenzodioxins and polychlorinated dibenzofurans as contaminants (IARC, 1983). Furthermore, certain polychlorinated dibenzodioxins and polychlorinated dibenzofurans have been associated with the types of cancer (lymphomas, sarcomas) seen in these studies (Hardell, 1979; Hardell et al., 1981; Eriksson et al., 1981). IARC (1983) concluded that these studies are not sufficient to evaluate potential human carcinogenic risk associated with exposure to MCPA alone.

Pertinent data regarding the carcinogenicity of MCPA or MCPB to experimental animals were not located in the available literature, and neither of these compounds is scheduled for carcinogenicity testing by the National Toxicology Program (NTP, 1983).

5.2. MUTAGENICITY

Both MCPA and MCPB have been tested in several genotoxicity assays. These assays are summarized in Tables 5-1 and 5-2, respectively.

MCPA gave negative results in most assays used, including reverse mutation assays with Salmonella typhimurium with and without exogenous metabolic activation (Moriya et al., 1983; Rasanen et al., 1977; Zetterberg,

TABLE 5-1

Genotoxicity of MCPA

Assay	Indicator Organism	Application	Concentration or Dose	Activation System	Response	Comments	Reference
Reverse mutation	Salmonella typhimurium TA98 TA100 TA1535 TA1537 TA1538	plate incorporation	<5000 µg/plate	±S-9	- - - - -	purity NR	Moriya et al., 1983
Reverse mutation	S. typhimurium TA98 TA100 TA1535 TA1537	plate incorporation	0.5-500 µg/plate	±S-9	- - - -	analytical grade (99.9% purity)	Rasanen et al., 1977
Reverse mutation	S. typhimurium TA98 TA100	plate incorporation	15-1000 µg/plate	±S-9	- -	Test compound was the methyl ester of MCPA, analytical grade.	Zetterberg, 1979
Forward mutation	Escherichia coli Gal R^s	spot test	NR	none	-	purity NR	Fahrig, 1974
Forward mutation	E. coli	liquid holding test	NR	none	-	purity NR	Fahrig, 1974
Reverse mutation	Serratia marcescens a 21 and a 742	spot test	NR	none	-	purity NR	Fahrig, 1974
Reverse mutation	Saccharomyces cerevisiae RAD 18	suspension culture	0.01×10^{-3} to 6×10^{-3} M	none	+	MCPA was positive only at pH <4.5, indicating that MCPA must be in the undissociated form to be taken up by the yeast cells. Also, MCPA elicited a positive response only at low cell survival levels (1-10%). The test compound was "free from impurities" (purity NOS).	Zetterberg, 1978a,b, 1979
Reverse mutation	S. cerevisiae	suspension culture	2.93×10^{-3} to 11.7×10^{-3} M	none	-	Test compound was the methyl ester of MCPA, analytical grade.	Zetterberg, 1979

TABLE 5-1 (cont.)

Assay	Indicator Organism	Application	Concentration or Dose	Activation System	Response	Comments	Reference
Mitotic gene conversion	S. cerevisiae RAD 18	suspension culture	NR	none	-	purity NR	Fahrig, 1974
Nondisjunction	Drosophila melanogaster	larval feeding	250 or 500 ppm	none	-	commercial product (94% purity)	Magnusson et al., 1977
Chromosome loss	D. melanogaster	larval feeding	250 or 500 ppm	none	-	commercial product (94% purity)	Magnusson et al., 1977
Induced X-Y recombination	D. melanogaster	larval feeding	250 or 500 ppm	none	-	commercial product (94% purity)	Magnusson et al., 1977
Sex-linked recessive lethal	D. melanogaster	adult exposure (route NR)	5.0 or 10.0 mM	none	+	Described as a "weak" mutagen, with the frequency of sex-linked recessive lethals increased "on the verge of significance," when data from several experiments for both exposure levels were pooled. Purity of test compound NR.	Vogel and Chandler, 1974
Host-mediated (reverse mutation)	S. typhimurium, G46; Serratia marcescens, Ng a 21	1.p. to NMRI mice	1000 mg/kg bw	mice (in vivo)	-	purity NR	Buselmaier et al., 1972; Fahrig, 1974
Micronucleus	mice/bone marrow cells	per os/cell culture	30, 100 or 200 mg/kg bw	mice (in vivo)	-	Purity NR. There was no increase in the percentage of micronucleated polychromatic erythrocytes.	Seiler, 1978
Chromosomal aberrations (translocations and chromsomal breaks)	human lymphocytes	cell culture	NR	none	-	purity NR	Fahrig, 1974

1.p. = intraperitoneal
NOS = Not otherwise specified
NR = Not reported

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TABLE 5-2

Genotoxicity of MCPB

Assay	Indicator Organism	Application	Concentration or Dose	Activation System	Response	Comments	Reference
Reverse mutation	Salmonella typhimurium TA98	plate incorporation	<5000 µg/plate	±S-9	-	purity NR	Moriya et al., 1983
	TA100				-		
	TA1535				-		
	TA1537				-		
	TA1538				-		
Reverse mutation	S. typhimurium 8 histidine-requiring strains, NOS	spot test	~1-5 µl	none	-	technical grade (≥90% purity)	Andersen et al., 1972
Forward mutation	Escherichia coli Gal R^s	spot test	NR	none	-	purity NR	Fahrig, 1974
Forward mutation	E. coli	liquid holding test	NR	none	-	purity NR	Fahrig, 1974
Reverse mutation	Serratia marcescens a 21 and a 742	spot test	NR	none	-	purity NR	Fahrig, 1974
Mitotic gene conversion	Saccharomyces cerevisiae	liquid holding test	NR	none	+	purity NR	Fahrig, 1974
Sex-linked recessive lethal	Drosophila melanogaster	adult exposure (route NR)	4.4 and 8.8 mM	none	-	purity NR	Fahrig, 1974
Host-mediated (reverse mutation)	S. typhimurium G46; Serratia marcescens Hy a 21	i.p. to NMRI mice	1000 mg/kg bw	mice (in vivo)	+,**	purity NR	Buselmaier et al., 1972; Fahrig, 1974

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TABLE 5-2 (cont.)

Assay	Indicator Organism	Application	Concentration or Dose	Activation System	Response	Comments	Reference
Dominant lethal	NMRI mice	i.p.	NR	none	-	purity NR	Fahrig, 1974
Chromosomal aberrations (translocations and chromosomal breaks)	human lymphocytes	cell culture	NR	none	-	purity NR	Fahrig, 1974

*MCPB was considered to be a "weak mutagen" in this host-mediated assay (Buselmaier et al., 1972; Fahrig, 1974).

i.p. = intraperitoneal

NOS = Not otherwise specified

NR = Not reported

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1979), forward mutation assays with Escherichia coli (Fahrig, 1974) and a reverse mutation assay with Serratia marcescens (Fahrig, 1974). MCPA did not elicit a positive response in the mitotic gene conversion assay with Saccharomyces cerevisiae (Fahrig, 1974). MCPA was negative in the nondisjunction, chromosome loss and induced X-Y recombination assays with Drosophila melanogaster (Magnusson et al., 1977). Negative results also were obtained for MCPA in a host-mediated assay using NMRI mice and S. typhimurium and S. marcescens (Buselmaier et al., 1972; Fahrig, 1974), in a mouse micronucleus assay (Seiler, 1978) and in a chromosomal aberrations (translocations and chromosomal breaks) assay with human lymphocytes (Fahrig, 1974).

The methyl ester of MCPA was negative in reverse mutation assays with S. typhimurium and S. cerevisiae (Zetterberg, 1979).

MCPA elicited positive responses in two assays, the reverse mutation assay with S. cerevisiae (Zetterberg, 1978a,b, 1979) and the sex-linked recessive lethals assay with D. melanogaster (Vogel and Chandler, 1974); however, each of these results must be viewed with caution because of special circumstances. First, in the reverse mutation assay with S. cerevisiae, MCPA elicited a positive response only at pH <4.5, indicating that MCPA must be in the undissociated form to be taken up by the yeast cells. Also, MCPA elicited a positive response only at low cell survival levels (1-10%). Second, in the sex-linked recessive lethals assay with D. melanogaster, MCPA was described as a "weak" mutagen, with the frequency of sex-linked recessive lethals increased "on the verge of significance," when data from several experiments for both exposure levels were pooled (Vogel and Chandler, 1974).

MCPB also gave negative results in most assays used, including reverse mutation assays with S. typhimurium (Moriya et al., 1983; Andersen et al., 1972) and S. marcescens (Fahrig, 1974) and forward mutation assays with E. coli (Fahrig, 1974). MCPB also yielded negative results in the sex-linked recessive lethals assay with D. melanogaster (Fahrig, 1974), the dominant lethal assay with NMRI mice (Fahrig, 1974) and a chromosomal aberrations (translocations and chromosomal breaks) assay with human lymphocytes (Fahrig, 1974).

MCPB elicited a positive response in the mitotic gene conversion assay with S. cerevisiae (Fahrig, 1974). MCPB was considered to be a "weak mutagen" in the host-mediated assay with NMRI mice and S. typhimurium and S. marcescens (Buselmaier et al., 1972; Fahrig, 1974).

5.3. TERATOGENICITY

In an unpublished study reported by U.S. EPA (1982), Irvine et al. (1980) administered technical grade MCPA at levels of 0, 20, 50 or 125 mg/kg to pregnant Sprague-Dawley rats; neither the exposure route nor the duration was reported in the summary. Minimal maternal toxicity and significantly decreased litter weights were reported for all treated groups. There were no treatment-related effects on pregnancy incidence, maternal weight gain, mean number of corpora lutea, preimplantation losses, implantations, early or total intrauterine deaths, number of fetuses per dam or the sex ratio.

The incidence of both major and minor external/visceral fetal defects at all dose levels was similar to the incidence in control animals. Major external/visceral defects included encephalocele, craniorachischisis with anophthalmia, open eye, omphaloc, arthrogryposia and disphragmatic hernia. Minor external/visceral defects included skeletal and muscular anomalies,

dilated ureters, increased renal pelvic cavitation, increased subcutaneous hemorrhagic areas and minor skeletal defects. There were no major skeletal defects in treated or control animals.

Yasuda and Maeda (1972) administered technical grade (94.12% purity) ethyl ester of MCPA (4-chloro-2-methylphenoxyacetic acid ethyl ester; MCPEE) in the diet to pregnant Wistar rats (10-16/exposure level) at levels of 0, 40 or 2000 ppm on days 8-21 of gestation or 500 or 1000 ppm on days 15-21 of gestation. Based on food consumption data, corresponding doses were calculated to be 0, 2.7, 30, 60 or 100 mg/kg/day. Day 0 of gestation was designated as the day sperm cells were detected in the vaginal smear. About 75% of those dams given diets containing 0, 40 or 2000 ppm and all of those receiving 500 or 1000 ppm were killed on day 21 of gestation. The remaining dams were allowed to undergo natural parturition, in order to raise the pups to 6 weeks of age, at which time they also were examined for external and internal anomalies. When compared to control animals, dams receiving diets containing 500, 1000 or 2000 ppm MCPEE had reduced body weight gains. Significantly decreased food consumption was reported only for dams given the 2000 ppm diet. Increased fetal mortality and neonate mortality were reported for the highest exposure level. There were dose-related decreases in fetal weight and increases in the number of terata for the 1000 and 2000 ppm levels. The major fetal defects were cleft palate, ventricular septal defects and kidney anomalies. One neonate of a dam given a diet containing 2000 ppm had hydronephrosis. For this study, the NOEL for fetotoxicity and teratogenic effects in rats was reported to be 500 ppm (30 mg/kg/day).

U.S. EPA (1982) also reported the results of an unpublished teratogenicity study in mice (Palmer and Lovell, 1971). Palmer and Lovell (1971) administered the commercial formulation Horotex 750, which contains 75% w/w

MCPA (75% purity), at doses of 0, 5, 25 or 100 mg/kg bw to pregnant mice (20/dose level) by gastric intubation on days 6-15 of gestation. The only toxic effect to dams was decreased body weight gain at the 100 mg/kg level. Fetotoxicity, manifested in significantly depressed litter weights and mean fetal weights, was observed only at the 100 mg/kg level. A significantly increased incidence of minor skeletal variants also was observed at the highest dose level. This study yielded a NOEL of 25 mg/kg bw for mice, based on observed minor skeletal defects and depressed fetal body weights.

The U.S. EPA (1982) summarized a two-part unpublished teratogenicity study of technical grade MCPA that was conducted with rabbits by Tucker and Irvine (1978) and Irvine et al. (1980). Tucker and Irvine (1978) did a range-finding study, dosing pregnant rabbits by gavage with technical grade MCPA at dose levels of 0, 25 or 100 mg/kg bw on days 1-27 of gestation. There were no live fetuses at the 100 mg/kg level. No teratogenic effects were observed in the fetuses of dams given 25 mg/kg. Maternal deaths occurred in both control and treated animals as a result of lung congestion from improper gavage techniques.

Using dose data from the range-finding study of Tucker and Irvine (1978), Irvine et al. (1980) administered technical grade MCPA by gavage to groups of 15 pregnant rabbits at levels of 0, 5, 12, 30 and 75 mg/kg bw on days 6-18 of gestation. Improper gavage techniques again resulted in lung congestion in treated dams; however, this effect was apparently dose-related to MCPA treatment (U.S. EPA, 1982). Dams affected by lung congestion also had other thoracic pathologic changes, such as thoracic fibrous adhesions. There was no correlation between dams with pulmonary congestion and those giving birth to pups with terata. The observed teratogenic effects may have been related to stress, however, in that sharp room temperature changes

occurred throughout mating. U.S. EPA (1982), in its summary of this unpublished study, did not enumerate teratogenic or fetotoxic effects or associate these effects with specific dose levels.

5.4. OTHER REPRODUCTIVE EFFECTS

Elo and Parvinen (1976) studied the spermatogenetic effects of the sodium salt of MCPA (MCPA-Na) following oral administration to male Sprague-Dawley rats. Groups of 5-9 rats were given drinking water containing MCPA-Na (99.6% purity) at concentrations of 0, 100, 500, 1000, 2000 or 3000 ppm (corresponding to levels of 0, 3, 61, 112, 190 or 246 mg/kg/day, respectively, based on water consumption data) for 2 months ad libitum. The resultant spermatogenetic effects included degeneration alterations in 5-50% of the seminiferous tubules with loss of spermatids at 112 mg/kg/day, and degeneration alterations in >50% of the seminiferous tubules with occasional loss of spermatids and spermatocytes at 190 or 246 mg/kg/day. At doses <61 mg/kg/day, some histologic changes were observed in individual animals but these were not considered treatment related.

In a 13 week unpublished study in beagle dogs (4 males/group) performed by Holsing (1970) and summarized by U.S. EPA (1982), there was also evidence for MCPA induced testicular changes. The dogs were maintained on diets containing 0, 160, 320, or 640 ppm of technical grade MCPA which, based on food consumption, corresponds to doses of 0, 4, 8 or 16 mg/kg/day. Curtailed spermatogenic activity and varying degrees of tubular atrophy were observed at incidences of 1/4 control, 1/4 low-dose animals, 2/4 mid-dose animals and 3/4 high-dose animals. The NOEL for curtailed spermatogenic activity and tubular atrophy in dogs was considered to be 4 mg/kg/day by the U.S. EPA (1982).

Seiler (1979) examined the effect of MCPA on testicular DNA synthesis in male mice. The animals were given an intraperitoneal dose of [^{14}C]-methyl labeled thymidine, followed 1 hour later by 200 mg MCPA/kg bw orally; [^{3}H]-methyl labeled thymidine was administered intraperitoneally 3 hours after administration of the test compound, and the animals were killed 0.5 hours later. Treatment with MCPA resulted in significant ($p<0.01$) inhibition of testicular DNA synthesis (54% inhibition).

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Verschuuren et al. (1975) administered MCPA (80.6% pure) ad libitum in the diet to weanling SPF-Wistar rats (10 of each sex/dose level) at concentrations of 0, 50, 400 or 3200 ppm for 90 days. Neither increased mortality nor histopathologic abnormalities related to treatment were observed. At the highest dose level, decreased body weight gain was accompanied by decreased food consumption. The only treatment-related effect on blood composition was significantly larger erythrocytes with proportionally more hemoglobin in both sexes receiving 3200 ppm MCPA. Animals at the highest dose level had decreased numbers of erythrocytes, but the depressed number was not statistically significant. No significant dose-related changes on measured clinical biochemical parameters were observed for any exposure group. Several relative organ weights were found to be significantly ($p<0.05$) increased at the 3200 ppm level; Verschuuren et al. (1975) indicated that these increases may have been related directly to decreased body weights. Relative increased organ weights at the highest dose level included the liver, kidneys, adrenals, thyroid and brain of females, and the kidneys, testes and brain of males. The relative kidney weights of both sexes also were significantly ($p<0.01$) increased at the 400 ppm level.

Gurd et al. (1965) administered the diethanolamine salt of MCPA at concentrations of 0, 100, 400, 1000 or 2500 ppm in the diet to rats (5 of each sex/dose level) for 7 months. Reduced body weight gain was reported for both sexes given the two highest dietary concentrations of MCPA diethanolamine salt. Food consumption for all treated groups was comparable to controls. For both sexes of rats on diets containing ≥400 ppm MCPA diethanolamine salt, reduced erythrocyte counts, hemoglobin and packed cell volume were observed. Increased liver-to-body-weight ratios occurred in females ingesting ≥400 ppm MCPA diethanolamine salt, but not in males at any dose level. Both sexes at all treatment levels had increased kidney-to-body-weight ratios. No treatment-related histological changes occurred in either sex at any treatment level.

U.S. EPA (1982) summarized two unpublished subchronic studies of dietary administration of MCPA to rats (Holsing and Kundzin, 1968, 1970). In the earlier study, Holsing and Kundzin (1968) administered technical grade MCPA in the diet to Charles River rats (10 of each sex/exposure level) at levels of 0, 25, 50 or 100 mg/kg/day for 90 days. There were no treatment-related effects on hematologic indices, biochemical parameters or urinalysis parameters at any dose level tested for either sex. Decreased body weight with accompanying decreased food consumption was reported for both sexes receiving 100 mg/kg/day. At unspecified exposure levels, significantly decreased organ weights were reported for the heart, liver, spleen, kidneys, thyroid, adrenals and testis with epididymus. U.S. EPA (1982), however, indicated that only the increased liver weight was considered to be treatment-related. Dose-related renal and hepatic cytopathologic changes at all treatment levels were observed during microscopic examinations. U.S. EPA (1982) concluded from this study that the NOEL for rats was <25 mg/kg/day.

In the later study, Holsing and Kundzin (1970) administered technical grade MCPA in the diet to Charles River rats (10 of each sex/exposure level) at levels of 0, 4, 8 or 16 mg/kg/day for 90 days. There were no treatment-related effects on mean body weights, food consumption, hematologic indices, biochemical parameters, urinalysis parameters or survival for either sex at any dose level tested. There was a significant increase in both kidney weight and the kidney-to-body-weight ratio for males at the highest exposure level, with a moderate increase for males at the two other treatment levels. There were no treatment-related histopathologic alterations in either sex at any dose level tested. The NOEL for increased kidney weights in rats was 8 mg/kg/day.

Hattula et al. (1977) administered the sodium salt of MCPA (MCPA-Na; 99% purity) to male Sprague-Dawley rats (5 or 6/exposure level) ad libitum in their drinking water at concentrations of 0, 100, 500, 1000, 2000 or 3000 mg/l for 9 weeks. Based on water consumption data, these exposure levels are equivalent to 0, 13, 61, 112, 190 or 246 mg/kg/day, respectively. Decreased body weights, accompanied by decreased water consumption, occurred at levels $\geq$1000 mg/l; food consumption data were not reported. Significantly increased relative organ weights included the liver at $\geq$100 mg/l, brain and adrenals at $\geq$1000 mg/l and kidneys at the two highest exposure levels. In all five groups of treated animals, there were a slightly decreased amount of white pulp in the spleen and focal degeneration of hepatic parenchymal cells. At MCPA-Na concentrations $\geq$1000 mg/l, loss of maturing spermatids and slight degenerative alterations in the seminiferous epithelium were observed.

U.S. EPA (1982) summarized two unpublished subchronic studies of dietary administration of MCPA to dogs (Holsing, 1968, 1970). In the earlier study,

Holsing (1968) administered technical grade MCPA in the diet to beagle dogs (3 of each sex/dose level) at levels of 0, 25, 50 or 100 mg/kg/day for 13 weeks. Body weight loss was reported for all three exposure levels; food consumption data were not provided in the U.S. EPA (1982) summary. Treatment-related effects on hematologic indices included decreased hemogram in one female after receiving the lowest MCPA concentration tested for 1 month; decreased hemograms, marked increase in band cells and a slight increase in metamyelocytes at the middle concentration level; and decreased hemograms in dogs given the highest concentration level. Treatment-related effects on biochemical parameters included increased BUN and SGOT and decreased serum potassium at all three treatment levels. In this study, the NOEL for dogs was <25 mg/kg/day.

In the later study, Holsing (1970) administered technical grade MCPA in the diet to beagle dogs (4 of each sex/dose level) at levels of 0, 160, 320 or 640 ppm (equivalent to 0, 4, 8 or 16 mg/kg/day, based on food consumption) for 13 weeks. There were no treatment-related effects on appearance, behavior, food consumption, hematologic indices or biochemical parameters. At the highest dose level, there were decreases in both the testes weight and the testes-to-body-weight ratio. Curtailed spermatogenic activity and varying degrees of tubular atrophy were seen at incidences of 1/4 control animals, 1/4 low-dose animals, 2/4 mid-dose animals and 3/4 high-dose animals. The NOEL for curtailed spermatogenic activity and tubular atrophy in dogs was considered to be 4 mg/kg/day by the U.S. EPA (1982).

5.6. OTHER RELEVANT INFORMATION

The oral LD_{50} of MCPA is 700 mg/kg in rats (NIOSH, 1983), 550 mg/kg in mice (NIOSH, 1983), 550 mg/kg in female guinea pigs (NAS, 1977) and 813 mg/kg in female rabbits (NAS, 1977). The intravenous LD_{50} of MCPA is 28

mg/kg in mice (NIOSH, 1983). The intraperitoneal LD_{50} of MCPA is 400 mg/kg in rats and 500 mg/kg in mice (NAS, 1977).

The oral LD_{50} of MCPB is 680 mg/kg in rats and 800 mg/kg in mice (NIOSH, 1983).

The oral LD_{50} of the sodium salt of MCPA is 560 mg/kg in mice (Gurd et al., 1964). The inhalation LD_{50} of the sodium salt of MCPA is 21.4 mg/ℓ in rats (Biesemeier and Argevine, 1977). MCPA sodium salt caused severe eye irritation (Raltech Scientific Services, Inc., 1977a) and mild skin irritation (Raltech Scientific Services, Inc., 1977b) in New Zealand rabbits.

The oral LD_{50} of the diethanolamine salt of MCPA is 800 mg/kg in rats and 550 mg/kg in mice (Gurd et al., 1964).

The butoxyethyl ester of MCPA caused mild eye irritation in rabbits (Gabriel, 1971).

Verschuuren et al. (1975) applied MCPA (80.6% pure) dermally as an aqueous paste to the shaved backs and flanks of groups of four male Chinchilla rabbits at levels of 0, 0.5, 1.0 or 2.0 g/kg bw, 5 times/week for 3 weeks. Decreased body weight gain and erythema were seen at all treatment levels. Treated rabbits had hyperplasia and hyperkeratosis of the skin. At the 1.0 g/kg level, three of four rabbits died, and at the 2.0 g/kg level, four of four rabbits died. Focal liver necrosis, renal tubular degeneration and marked lymphocyte depletion in the spleen and thymus were seen in animals at the two highest dose levels. The increased mortality and pathological lesions may have been a result of severe enteritis due to dysbacteria, rather than a result of MCPA treatment.

When administered intragastrically for 2 weeks, MCPA altered the hepatic and intestinal biotransformation activities of rats (Hietanen et al., 1983). Increased activities of hepatic and intestinal ethoxycoumarin O-deethylase

and epoxide hydrolase and decreased activity of hepatic glutathione S-transferase were seen in treated animals.

Oral administration of MCPB at a level of 1570 mg/kg to rats did not affect brain aminotransferase activity, but did result in redistribution of the different enzymic forms of hepatic aminotransferases at 3 hours after treatment (Nikandrov, 1974).

Rats pretreated with MCPA, followed by acute or chronic administration of [^{14}C]-MCPA, resulted in increased levels of [^{14}C]-MCPA in the brain and cerebrospinal fluid as compared to rats not pretreated but only given [^{14}C]-MCPA; the increased levels were thought to be indicative of blood-brain barrier damage as a result of the initial exposure (pretreatment) (Elo and Ylitalo, 1977, 1979; Hervonen et al., 1982; Elo et al., 1982).

Ataxia, neuromuscular irritability, convulsions, coma, renal and hepatic damage, aplastic anemia and acute leukemia as a result of ingestion of MCPA have been reported in human case studies (Bovey, 1980; Palva et al., 1975; Timonen and Palva, 1980; Popham and Davis, 1964; Johnson and Koumides, 1965; Jones et al., 1967). Voluntary ingestion of 5 mg MCPA by each of four male volunteers (ages 32-36 years; described as being healthy) did not cause liver or muscle damage (Fjeldstad and Wannag, 1977).

6. AQUATIC TOXICITY

6.1. ACUTE

The acute toxicity of MCPA has been investigated with at least eight species of freshwater or marine animal species (Table 6-1). The acute toxicity of MCPB has been determined for three species of freshwater animals (Table 6-2).

The data in Table 6-1 indicate that acute LC_{50} values for MCPA ranged from 89-163.5 mg/ℓ for four freshwater fish species and that acute toxic effects were not observed in other freshwater species at concentrations <89 mg/ℓ. The U.S. EPA (1982) cited five studies showing that the 24% sodium salt formulation of MCPA had LC_{50} values ranging from 180->1000 ppm for freshwater fish. The individual LC_{50} values and fish species were not specified in this report. Similarly, the U.S. EPA (1982) cited the results of five studies showing that the LC_{50} values of the 52% dimethylamine salt formulation of MCPA were >180 ppm for bluegills and trout.

In contrast, the available data (see Table 6-1) for marine species indicate that MCPA was acutely toxic to oyster eggs at 15.6 mg/ℓ (Davis and Hidu, 1969) and to blue crabs at 5.0 ppm (Butler, 1963).

Although acute toxicity data for both chemicals are limited, it appears that MCPB is more toxic than MCPA. Dive et al. (1980) reported that 10 ppm MCPB was the minimum toxic dose to a protozoan species, whereas MCPA had no toxic effect at 10 ppm. Similarly, the acute LC_{50} value for bluegill was 97 or 163.5 mg/ℓ for MCPA (Schneider, 1979; Davis and Hughes, 1963) and 15 mg/ℓfor MCPB (Davis and Hardcastle, 1959).

6.2. CHRONIC

The only available data concerning the chronic toxicity of MCPA or MCPB to aquatic organisms were provided by Davis and Hidu (1969), who conducted a

TABLE 6-1

Acute Toxicity of MCPA to Aquatic Animals

Species	Duration (hours)	Concentration (ppm)	Effect	Reference
FRESHWATER				
Protozoan, Colpidium campylum	43	10	no effect	Dive et al., 1980
Waterflea, Daphnia magna	26	>100[a]	LC_{50}	Crosby and Tucker, 1966
	48	180[b]	20% mortality	Schneider, 1979
Rainbow trout, Salmo gairdneri	96	89-91[b]	LC_{50}	Schneider, 1979
Brown trout, Salmo trutta	24	147[c]	LC_{50}	Hattula et al., 1979
Bluegill, Lepomis macrochirus	96	97[b]	LC_{50}	Schneider, 1979
	48	163.5[d]	LC_{50}	Davis and Hughes, 1963
	100	10[e]	no effect	Cope, 1963
MARINE				
Oyster (eggs), Crassostrea virginica	48	15.6	LC_{50}	Davis and Hidu, 1969

TABLE 6-1 (cont.)

Species	Duration (hours)	Concentration (ppm)	Effect	Reference
Oyster (adults), Crassostrea virginica	96	1.0[e]	no effect	Butler, 1965
Blue crab, Callinectes sapidus	48	5.0[e]	sublethal irritation	Butler, 1963
Longnose killifish, Fundulus similis	48	75.0[e]	no effect	Butler, 1963

[a]Acid, technical standard

[b]Technical acid, 94%

[c]Sodium salt, 88%

[d]Alkyl amine

[e]Amine

TABLE 6-2

Acute Toxicity of MCPB to Aquatic Animals

Species	Duration (hours)	Concentration (ppm)	Effect	Reference
FRESHWATER				
Protozoan, *Colpidium campylum*	43	10	minimum active dose	Dive et al., 1980
Bluegill, *Lepomis macrochirus*	48	15*	LC_{50}	Davis and Hardcastle, 1959
Largemouth bass, *Micropterus salmoides*	48	10*	LC_{50}	Davis and Hardcastle, 1959

*Dimethylamine salt

14-day toxicity test with oyster, Crassostrea virginica, larvae. The 14-day LC_{50} value of MCPA was 31.3 ppm.

6.3. PLANT EFFECTS

The effects of MCPA and MCPB have been investigated with several species of freshwater and marine plants. Kirkwood and Fletcher (1970) compared the toxicity and absorption of MCPA and MCPB in three freshwater algal species at three pH levels. Chlamydomonas globosa, Chlorella pyrenoidosa and Stichococcus bacillaris were exposed to 10^{-4} and 10^{-3} M MCPA or MCPB at pH 5.0, 6.5 or 8.0. MCPB inhibited growth, respiration and phosphate uptake to a greater extent than MCPA, and was toxic to all three species at 10^{-4} M (22.9 mg/ℓ) at one or more pH levels. Exposure to 10^{-4} M MCPA (20.1 mg/ℓ) caused little, if any, growth inhibition of C. globosa and C. pyrenoidosa. The growth of S. bacillaris was inhibited by 10^{-4} M (20.1 mg/ℓ) of MCPA at pH 5.0 and 6.5. At pH 8.0, both MCPA and MCPB at 10^{-4} M caused growth stimulation of S. bacillaris. Toxicity and uptake of MCPA and MCPB generally decreased with increasing pH.

The effects of MCPA on marine plants have been investigated by Butler (1963) and Hopkin and Kain (1978). Butler (1963) reported that exposure to 1.0 ppm of MCPA amine (MCP Amine Weed Killer) for 4 hours had no effect on carbon incorporation in natural marine phytoplankton communities. Hopkin and Kain (1978) exposed seaweed (Laminaria hyperborea) fronds, sporophytes and gametophytes to MCPA, and reported that the most sensitive effect was growth inhibition of sporophytes at a MCPA concentration of 100 ppm.

6.4. RESIDUE

Although data concerning MCPA and MCPB residues in wild aquatic organisms were not located, the available experimental evidence indicates that MCPA is not bioconcentrated. Slyn'ko (1981) reported that exposure of trout

and tubificid worms to a MCPA formulation (2M-4Kh) at 16 ppm resulted in tissue concentrations of 1.2 and 0.8 ppm, respectively. Hattula et al. (1979) exposed brown trout, Salmo trutta, to 10 and 30 ppm of the technical grade sodium salt of MCPA (88%) for 28 days, during which the exposure solutions were renewed daily. The average wet tissue concentrations were 3.08 and 4.06 ppm in fish exposed to 10 and 30 ppm, respectively. Both of these studies indicate that the BCF was <1, indicating that bioconcentration did not occur.

6.5. OTHER RELEVANT INFORMATION

The available data indicate that the uptake and toxicity of MCPA and MCPB may be related to pH. Kirkwood and Fletcher (1970) reported that the toxicity and uptake of MCPA and MCPB in three unicellular algae species generally decreased with increasing pH. Truelle (1961) reported that the acute toxicity of Dicotex (containing sodium salt of MCPA) to fish decreased substantially at weakly alkaline pH, relative to neutral pH. These results may be explained by the fact that uptake of these acids will be greater at the lower pH levels, favoring movement as the undissociated molecule.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The current tolerances for residues in or on raw agricultural commodities for MCPA or its sodium, ethanolamine, diethanolamine, triethanolamine, diisopropanolamine, triisopropanolamine or dimethylamine salts or its isooctyl or butoxyethyl esters has been established by the U.S. EPA (Code of Federal Regulations, 1983). These tolerances range from 300 ppm for pasture and rangeland grass, to 0.1-20 ppm for grains and forage producers, and 0.1 ppm (negligible residues) for animal meats and fats. These tolerances are for MCPA and its metabolites 2-methyl-4-chlorophenol.

U.S. EPA (1982) calculated a provisional ADI of 0.002 mg/kg/day (equivalent to 0.14 mg/day for a 70 kg human), based on a NOEL of 4 mg/kg/day for spermatogenic effects in beagle dogs (see Section 5.5.) (Holsing, 1970) and an uncertainty factor of 2000.

7.2. AQUATIC

Pertinent data regarding guidelines and standards for MCPA and MCPB in the aquatic environment were not located in the available literature. (See Appendix for literature searched; also additional classified information is available. See Chapter 8 for a more complete explanation.)

8. RISK ASSESSMENT

Several studies exist that examine the relationship between concurrent human exposure to several phenoxyacetic acid herbicides, including MCPA, and cancer (Hardell, 1979; Hardell et al., 1981; Eriksson et al., 1981; Barthel, 1976). IARC (1983) concluded, however, that these studies are not sufficient to evaluate potential human carcinogenic risk associated with exposure to MCPA alone. Neither MCPA nor MCPB has been tested for carcinogenicity in experimental animals.

Both MCPA and MCPB elicited negative responses in many different genotoxicity assays (see Section 5.2.), and only a couple of weakly mutagenic responses were obtained for each compound (Zetterberg, 1978a,b, 1979; Vogel and Chandler, 1974; Fahrig, 1974; Buselmaier et al., 1972).

Yasuda and Maeda (1972) administered the ethyl ester of MCPA orally to pregnant rats and found a NOEL of 30 mg/kg bw/day for fetotoxicity and teratogenic effects. Following oral administration to pregnant mice, Palmer and Lovell (1971) reported a NOEL of 25 mg/kg bw/day for minor skeletal defects and depressed fetal body weights.

Elo and Parvinen (1976) found varying degrees of degeneration of the seminiferous tubules with or without the loss of spermatids and spermatocytes in male rats given drinking water containing the sodium salt of MCPA at levels of 0, 3, 61, 112, 190 or 246 mg/kg bw/day. There was no clear dose-related response among the treated groups of rats. MCPA administered orally at a level of 200 mg/kg bw to male rats resulted in significant ($p<0.01$) inhibition of testicular DNA synthesis (54% inhibition) (Seiler, 1979).

Several subchronic dietary studies of MCPA in rats and dogs have been completed (Verschuuren et al., 1975; Gurd et al., 1965; Holsing and Kundzin, 1968, 1970; Holsing, 1968, 1970). The study by Verschuuren et al. (1975) yielded a NOEL for MCPA to rats of 50 ppm for increased relative kidney weight, while the Gurd et al. (1965) study gave a LOAEL for MCPA diethanolamine salt to rats of 100 ppm for increased kidney-to-body weight ratios. Holsing and Kundzin (1968), in a preliminary study, found a NOEL for MCPA to rats of <25 mg/kg bw/day for renal and hepatic cytopathologic changes. In the later study, Holsing and Kundzin (1970) reported a NOEL for MCPA to rats of 8 mg/kg bw/day for increased relative kidney weights and increased kidney-to-body weight ratios among males.

Holsing (1968), in a preliminary study with dogs, found a NOEL for MCPA of <25 mg/kg bw/day based upon hematologic and biochemical effects. In a 13-week study using dogs, Holsing (1970) reported a NOEL of 4 mg MCPA/kg bw/day for curtailed spermatogenic activity and tubular atrophy. At the higher dose levels of 8 and 16 mg/kg bw/day, 50 and 75% of the dogs, respectively, were reported to have decreased spermatogenic activity and tubular atrophy, although the number of dogs used (4 animals/dose), was small. The study using rats by Elo and Parvinen (1976), provides supportive evidence that MCPA has the potential to adversely effect spermatogenesis. In this study, daily doses of 112 mg/kg bw/day for 2 months were reported to produce seminiferous tubule degeneration, while at lower doses of 61 and 3 mg/kg bw/day no clear effect was observed.

Using the NOEL of 4 mg/kg bw/day from the study by Holsing (1970), an ADI of 0.28 mg/day (0.004 mg/kg bw/day) can be derived by multiplying by the assumed body weight of a human, 70 kg, and dividing by an uncertainty factor of 1000 (10 to convert from experimental animal data to human data, 10 for the use of a subchronic study for human ADI derivation, and 10 for protection of the most sensitive individuals within the human population).

The lack of any published cancer assays and chronic or subchronic toxicity studies precludes the derivation of a quantitative risk assessment value for MCPB.

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential data, which this document could not address, are not in existence. These data, which are considered Confidential Business Information (CBI), are available in summary form as a CBI Appendix that can be accessed by individuals with appropriate clearance. Conclusions from the CBI Appendix regarding risk assessment can, however, be presented in this chapter.

The CBI Appendix to this document reviews other animal data that indicate that a more conservative ADI for MCPA should be adopted. An ADI of 0.001 mg/kg bw/day, or 0.07 mg/day for a 70 kg man, is recommended, based on a NOAEL of 1.0 mg/kg bw/day for kidney effects (elevated BUN) in dogs in a 13-week feeding study and using an uncertainty factor of 1000 (10 for interspecies extrapolation, 10 for protection of unusually sensitive individuals within the human population, and 10 to account for the use of a subchronic NOAEL for ADI derivation).

The CBI Appendix also reviews subchronic studies of MCPB in animals. A NOEL of 4.0 mg/kg bw/day in a 13-week feeding study in rats was considered to be too close to the LOAEL of 5.1 mg/kg bw/day for elevated BUN, SGOT and BSP retention in dogs in a 13-week feeding study to be used to derive an ADI for MCPB. Since the target organs (liver, kidney) for the toxicity of MCPA and MCPB are the same, and since the toxicities based on mortality data are similar, it is recommended that the ADI of 0.001 mg/kg bw/day (0.07 mg/day for a 70 kg adult human) for MCPA be considered as sufficiently protective against the toxic effects of MCPB as well.

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE

These searches were conducted in November, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7th), and the following secondary sources were reviewed:

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